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<p>The goal of the research has been to determine whether there is evidence of a diffusible coupling signal from the Suprachiasmatic Nucleus. If a diffusible signal is physiologically significant, it has the potential for use as a bioactive agent for exogenous administration. We believe we now have evidence that such a signal exists, and that it can appear in biologically significant amounts in the cerebrospinal fluid. At the present time we are working to complete the most definitive experiments providing such proof. We are also working towards our next goal: to establish the experimental conditions for identifying the diffusible signal.</p>			
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## **I. Annual technical report**

### **I.a Statement of research objectives**

Signals from the suprachiasmatic nucleus (SCN) serve to entrain daily biological rhythms in a great number of physiological and behavioral responses. Previous research has focused on the role of neural efferents in regulating circadian rhythmicity, while the potential role of diffusible signals has been largely ignored. This is an important question, both pragmatically and theoretically. If a diffusible signal is physiologically significant, it could be developed for use as a bioactive agent for exogenous administration. The **overall** objective of the present work is to determine whether there is a diffusible coupling signal from the biological clock, located in the SCN of the mammalian brain. optimize conditions for graft survival and development within the capsule.

### **I.b Status of the research.**

In one series of (completed, in press) experiments, we have used the 2-DG technique to assess the ability of donor SCN grafts to synchronize its metabolic activity with the host SCN. Such synchronization would suggest a diffusible signal from the SCN has a coupling function. The time course of the synchronization of donor and host would indicate the rate of resetting of the biological clocks. In a series of (completed, in preparation) studies, we have found that the precision of a circadian rhythm that is restored following implantation of SCN grafts, is dependent on the distance of the graft from the site of the lesioned host SCN. The results support the notion of a locally diffusible signal in the SCN. In another series of (ongoing) experiments, we have used encapsulated SCN tissue taken from (wild type) donor animals implanted into (tau mutant) host animals and have found restoration of circadian rhythmicity in 3 animals. While these results are strong evidence for the presence of a diffusible signal, the encapsulation technique must be improved as the restoration rate is low. Improvement of the methodology will set the stage for identification of the diffusible factor. The foregoing evidence for a diffusible signal in the CSF has encouraged us to explore the use of timed transfusions of CSF from donor to host animal. Such studies would also provide support for the existence of a diffusible signal and would set the stage for its isolation. To summarize, we have strong evidence that the SCN produces a diffusible signal. The research effort is now being directed at establishing conditions which will permit identification of that signal.

### **I.c Written publications**

Silver, R. "Rapporteur for chapter on "Cellular basis of clocks". Edited by J. Dunlap and J. Loros (in preparation for 1995)

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Serviere, J., Gendrot, G. LeSauter, J. and R. Silver (in press). Host resets phase of grafted SCN: I. A 2-deoxyglucose study of the time course of entrainment. *Brain Res.*

Serviere, J., Gendrot, G. LeSauter, J. and R. Silver (in press). Host resets phase of grafted SCN: II. Influence of implant site, tissue specificity, and pineal secretions. *Neurosc. Lett.*

Lehman. M.N. and R. Silver (1994). Restoration of circadian rhythms by neural transplants. *Neuronal Transplantation, CNS Neuronal Injury and Regeneration.* (Eds. J. Marwah, P. Teitelbaum, and K.N. Prasad.) CRC Press Inc. pp 141-160.

LeSauter, J. and R. Silver (1994) Suprachiasmatic nucleus lesions abolish and fetal SCN grafts restore circadian gnawing rhythms in hamsters. *Restorative Neurol. and Neurosc.* 6: 135-143.

Silver, R. and J. LeSauter. (1993). What do SCN transplants do? *Brain Res. Reviews* 18: 322-325.

Silver, R. and J. LeSauter (1993). Efferent signals of the suprachiasmatic nucleus. *J. Biol. Rhythms (Supplement)* 8: S89-S92

### **I.e Interactions**

#### **I.e.i papers presented**

Silver, R. (7/95) Cellular basis of clocks. American Physiological Society. Dartmouth.

Silver, R. (4/95) Encapsulated SCN grafts. Keystone Symposium, Colorado

LeSauter J., P. Romero, and R. Silver (1994). Location of SCN graft influences precision of recovered circadian rhythm. *Soc. Res. Biol. Rhythms Abstr.* 4 34.

Roniero, M.T., J. LeSauter, P. Romero, M.N. Lehman, and R. Silver (1994). Restoration of function: Principles derived from studies of suprachiasmatic nucleus (SCN) transplants. *Am. Soc. Neural Transplantation Abstr.* 1:12.

Lehman, M.N., J. LeSauter, C. Kim, S.J. Berrian, P. Tresco, and R. Silver (1994). How do grafts of the suprachiasmatic nucleus communicate with the host brain? *Am. Soc. for Neural Transplantation Abstr.* 1:12.

Romero, P., J. LeSauter, and R. Silver (5/1994). Distance of SCN graft from lesion site influences precision of recovered circadian activity

rhythm. New England Consortium for Undergraduate Science Education (NECUSE). Student Workshop on photoperiodism, rhythms and clocks.

M.D. Cascio, J. Le Sauter, and R. Silver (5/1994). Intact vs. grafted SCN: comparison of VIP and VP-ergic fiber projections. New England Consortium for Undergraduate Science Education (NECUSE). Student Workshop on photoperiodism, rhythms and clocks.

Silver R., J. Le Sauter, C. Kim, M. Lehman (5/1994). How do fetal grafts of the suprachiasmatic nucleus communicate with the host brain? 5th International Symposium on Neural Transplantation.

Serviere, J., G. Gendrot, J. LeSauter and R. Silver (1993). When does host reset grafted SCN? Influence of implant site, tissue type and pineal secretions. Soc. Neurosci. Abstr. 19 1615.

Besmer, R.H., R. Khan, J. Nunez, J. LeSauter and R. Silver.(1993) A distinct subnucleus of calbindin-11 immunoreactive cells in the hamster suprachiasmatic nuclei. Soc. Neurosci. Abstr. 19 1613.

Silver, R. (8/1993) What do SCN transplants do? Gordon Conf. Vermont.

Silver, R. (12/1993) Lessons from SCN grafts. University of Virginia at Charlottesville.

Silver, R. (4/1993) Efferent signals of the SCN: lessons from neural grafting studies. International Conference on the Cellular Consequences of Sleep, Hawaii.

#### **I.e.ii consulting and advisory functions**

1994-1998: NIMH Psychobiology, Behavior, and Neurosciences Panel Member

1995: American Physiological Society, Conference on "Understanding the Biological Clock - from Genetics to Physiology", Rapporteur.

1994-1999: Associate Editor, Journal of Biological Rhythms

1994-1997: Advisory Committee, General Clinical Research Center, University of Virginia, Department of Medicine

1994-1996: Member-at-Large: Soc. Res. Biol. Rhythms

1994: Site visit panel member: NIH review of program project grant at Morehouse School of Medicine

1993-94: NIMH Behavioral Neurosciences Panel Member

1993: NSF Site visit of Center for the Study of Biological Rhythms, University of Virginia

1993: APA, Program Chair

1992: Society for Research in Biological Rhythms, Advisory Committee

1991-2000: Chair of External Advisory Committee, NSF Center for the Study of Biological Rhythms, University of Virginia

**I.f New Discoveries/inventions**

None

**I.g Other comments on progress**

We have been working closely with Dr. Patrick Tresco at the University of Utah to improve the biocompatibility of polymer capsules for use in tissue transplantation. The general strategy is two-fold. On the one hand we are working to improve the capsule material. On the other hand we are exploring the role of neurotrophic factors in enhancing tissue survival. This work has potential not only for furthering the understanding of the circadian system, but also for the development of encapsulated materials for other biological (both neural and non-neural) tissues.